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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,953	09/27/2000	Claude Meares	2307O-099120US	8313

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,953	MEARES ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,10,11,14-25,30-38 and 42-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *10 and 11* is/are allowed.

6)☒ Claim(s) *1-3,14-25,30-38 and 42-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Request for Continued Examination

1. The request filed on 8/25/03 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/671,953 is acceptable and a RCE has been established. Claims 1-3, 10-11, 25, 30-38, 42-44 are pending and are currently under prosecution. An action on the RCE follows.

2. Claims 1, 14, 22, 25, 42-43 have been amended and claim 44 has been added.

3. Claims 1-3, 10-11, 14-25, 30-38 are under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. The following Office Action contains NEW GROUNDS of rejections.

Claim objection

6. Claim 43 is objected to because the claim contains the phrase "complementarity-determining region regions". It appears that the term "region" is redundant.

Rejection Withdrawn

7. The rejection of claim 14 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily

available to the public; (2) reproducible from the written description is withdrawn in view of the amendments to the claim and the completion of the deposit requirements for the antibody ATCC Deposit No. PTA-4696 in paper number 18, filed 10/28/02.

8. The rejection of claims 1-3, 14-25, 30-38, and claims 42-43 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendments to the claims.

9. The rejection of claims 14 under 35 U.S.C. 102(b) as being anticipated by Stickney et al (Cancer Research 51:6650-6655, 1991, IDS #7) is withdrawn in view of the amendments to the claims.

10. The rejection of claim 14 under 35 U.S.C. 103(a) as being unpatentable over Reardan et al (Nature 316:265-267, 1985, IDS #7) and further in view of Orlandi et al (Proc. Natl. Acad. Sci. USA 86:3833-3837, 1989) and Pastan et al (U.S. Patent 5,747,654, issued 5/5/98, IDS #8) and Goodwin et al (The Journal of nuclear medicine 29:226-234, 1988, IDS #7) is withdrawn in view of the amendment to the claim.

Response to Arguments

11. The rejection of newly added claim 44 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is maintained and made again.

The newly added claim is essentially as that of previous claim 14 and recites the mutant antibody according to claim 1, wherein said mutant antibody is a mutant of CHA255. This claim is rejected for the same reasons claim 14, prior to this amendment (8/25/03), was rejected.

The claim requires the CHA255 antibody in order to practice the invention. The claim requires a mutant of CHA255 which encompasses a genus of mutants. This rejection would be obviated by either reciting in the claim the antibody of claim 1 wherein the antibody is S95C and the deposit number from the ATCC for this cell line or depositing the CHA255 antibody cell line.

12. The rejection of claims 1-3, 16-19, 24, 42, and newly added claim 44 under 35 U.S.C. 102(b) as being anticipated by Stickney et al (Cancer Research 51:6650-6655, 1991, IDS #7) is maintained.

The response filed 8/25/03 has been carefully considured but is deemed not to be persuasive. The response states that as discussed in the interview of March 17, 2003, Stickney et al describes a (Fab')2 bifunctional antibody coupled by a stable thioether linkage and Stickney does not describe or mention any mutant antibodies and the antibody does not have a reactive site that is the mutation or a reactive site that reacts with carboxyl groups (see page 8 of response). In response to this argument, Stickney et al does describe a mutant antibody because the (Fab')2 is by combining the binding sites of two separate antibodies to create a mutant antibody. In addition, the addition of the linker would broadly be a mutation wherein a mutation can be a chemical

alteration of the protein or addition of a linker and the linker does have a reactive site that can interact with carboxyl groups as stated in the previous Office Action because the linker is a bis-maleimidomethyl ether and the linker would be a reactive site for acids, for example. The claims require a reactive site and the art of Stickney teach a linker with a reactive site.

Amending the claims to require an antibody wherein the antibody binds a metal chelate wherein said antibody has a SH group proximate to a CDR which is not present in the wildtype antibody and wherein the SH group forms a covalent bond with a reactive group on the chelate when bound to the antibody would obviate this rejection.

13. The rejection of claims 1-3, 16, 17, 18, 19, 20, 22, 23, 24, 25, 30, 31, 32, 33, 34, 37, 38, 42-43, and 44 under 35 U.S.C. 103(a) as being unpatentable over Reardan et al (Nature 316:265-267, 1985, IDS #7) and further in view of Orlandi et al (Proc. Natl. Acad. Sci. USA 86:3833-3837, 1989) and Pastan et al (U.S. Patent 5,747,654, issued 5/5/98, IDS #8) and Goodwin et al (The Journal of nuclear medicine 29:226-234, 1988, IDS #7) is maintained.

The response filed 8/25/03 has been carefully considured but is deemed not to be persuasive. The response states that the combination of references fails to disclose each element of the claimed invention and the response then addresses each reference (see page 10 of response). The response states that Reardan et al does not suggest a mutant antibody comprising a reactive site not in the wild-type antibody and Orlandi et al does not suggest a mutant antibody and Pastan et al does not suggest a mutant

antibody comprising a reactive site not present in the wild-type and wherein the CDRs recognize a metal chelate and Goodwin et al does not suggest a mutant antibody comprising a reactive site and the antibody of Goodwin et al does not bind a chelate comprising a reactive functional group of complementary reactivity to the reactive site (see pages 10-11 of response). In response to these arguments, Pastan et al clearly teaches a disulfide stabilized antibody and the antibody comprises a SH group not present in the wildtype antibody. As stated above the claims require a "reactive site" and the disulfide stabilized antibody has a reactive group because the disulfide bond would react with a reducing agent or reacts with another SH which was added in the method of Paston. With regard to Goodwin et al Goodwin et al clearly teaches a chelate comprising a reactive functional group of complementary reactivity to the reactive site (see figure 1). In addition, it appears as though the arguments are directed to the references separately and this rejection is based on a combination of references as stated in the previous Office Action.

The response states that there is no motivation to combine the references and the rejection is based on hindsight (see page 11-12 of response). In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*,

443 F.2d 1392, 170 USPQ 209 (CCPA 1971). It would have been obvious to produce the claimed invention because Pastan et al teaches the antibodies can be stabilized for greater stability and have small size and reach there target more rapidly and cleared quicker for targeting and imaging application (see column 2, lines 49-55) and Goldwin et al antibody is used for imaging and it would have been obvious to stabilized Goodwin et al antibody by the method of Pastan et al for the reasons states by Pastan. The response then addresses this statement and states that neither Paston nor Goodwin contain any mention of a mutant antibody having a reactive site not present in the wild-type wherein the mutation is the reactive site and interacts with sulfhydryl groups (see page 11-12). In response to this argument, as stated above Paston clearly teaches a mutant antibody with a reactive site that is not in the wild-type by adding a cysteine that reacts with another cysteine either in the protein or can react with another SH by reduction.

The response further states that one of skill in the art would not have a reasonable expectation of success to modify the references (see page 13 of response) and Paston et al contains no suggestion that a reactive group on a mutant antibody may be placed in a location that would allow the reactive site on the antibody to react with a reactive group on a metal chelate bound by the antibody (see page 13 of response). In response to this argument, the claims do not recite the limitation a reactive site reacting with the metal chelate.

The response further states that the rejection of claims 17 and 31 is based on erroneous interpretation (see pages 13-14 of response) and the targeting moiety and

the antibody are not the same. In response to this argument, there is nothing in the claims that requires the antibody and the targeting moiety to not be the same.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The following are NEW GROUNDS of rejection

Claim Rejections - 35 USC § 112

14. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is indefinite because it is unclear if the serine 95 of the light chain which is substituted by a cysteine is the mutation in claim 1 (and claim 14) or if it is an additional mutation.

15. Claims 1-3, 14-25, 30-38, 42-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutant antibody that comprises a reactive site that is the SH group of cysteine and is not present in the wild type parent antibody wherein the mutant antibody comprises 6 CDRs and specifically binds to a metal chelate wherein the reactive site is in a position proximate to a CDR, does not reasonably provide enablement for a mutant antibody that contains just any reactive site or the reactive site is in a CDR. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 15 is included in this rejection due to the indefinite nature of the claim because it is not clear if the S95C is the mutation in the PTA-4696 or if additional mutations in the CDRs are contemplated.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to an antibody that comprises a reactive site that is any reactive group and that is in a CDR of the antibody. The specification teaches an antibody which has been engineered to contain a cysteine residue at position 95 and 96 in the light chain of a CHA255 antibody which bind a metal chelate. The specification does not enable an antibody as broadly claimed which can have any reactive site that can be any reactive group or a reactive site added to any CDR.

The claims are broadly drawn to alterations in the residues in the CDR and it is well known that antibodies are made up of CDRs and it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which

consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979, PTO-892, Attach to paper #14). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that an antibody as defined by the claims which may contain mutations in the CDRs, have the required binding function. The specification does not teach addition of any amino acids containing just any reactive group in the CDRs of the antibody as broadly defined in the claims. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of predictability in the art as evidenced by Rudikoff et al and in view of the lack of guidance in the specification and in view of the broadly claimed invention, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Conclusion

16. Claims 10 and 11 are in condition for allowance.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879